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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/831,820 | 06/05/2001 | Giuseppe Locatelli | 1303-122 | 9636 |

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| EXAMINER |
|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/831,820 | LOCATELLI ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *25 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *11-13,15,16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Sequence Rules*

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the sequences in the specification are not properly identified by SEQ ID NO. Correction is required. It is noted that the CRF is fine and computer searching of this case was performed.

2. This objection is maintained. Table 1 in the specification at pages 12-15 is not correctly labeled with SEQ ID Nos for each sequence. Consequently, the specification still fails to comply with the Sequence Rules. Correction is required.

### *Election/Restrictions*

3. In view of the restriction requirement, which was made final in the previous office action, non-elected Groups and species are withdrawn. Consequently, claims 11-13, 15, 16 and 18 are withdrawn as drawn to non-elected subject matter.

### *Claim Rejections - 35 USC § 101*

4. Cancellation of claim 17 renders the 101 rejection moot.

### *Claim Objections*

5. The objection to claims 4-16 is withdrawn in view of the amendment.

### *Claim Rejections - 35 USC § 112*

6. The rejection of claims 1-3 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

However, with regard to the word "randomized", in claim 1 or 2, this word is still interpreted broadly as referring to any altered sequence which meets the structural requirements imposed by the claim.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al (Genome Research (1996) 6:995-1001) in view of WalkerPeach et al (U.S. 6,395,470).

Gibson teaches a method for the quantitative detection of a nucleic acid target from a sample (abstract), comprising the steps:

(a) extraction of the target nucleic acid from the sample (page 1000, column 2, subheading "RNA extraction")

(b) mixing under conditions suitable for a polymerization reaction (page 1000, column 2, subheading "QC RT-PCR") (Gibson expressly teaches that "Assay throughput could be increased by adding both probes to the same RT-PCR tube (page 999, column 1)".)

(i) the extracted target nucleic acid and calibrator (ie internal control) where the calibrator (internal control) can be designed by "scrambling of the internal sequence" (see page 995, column 1) and where the calibrator should "contain similar guanine + cytosine (G+C) content and be of equal or similar length" (see page 995, column 1) (for mixing see page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1) where preservation of the same G+C content will inherently preserve the sequence,

(ii) forward and reverse primers which anneal to regions on both the target and calibrator nucleic acids, (page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1) ,

(iii) probes that are doubly labeled with reporter and quencher fluorophores that hybridize to the target nucleic acid and the calibrator (page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1)

(iv) a nucleic acid polymerase with a 5'-3' nuclease activity (page 1000, column 2, subheading "QC RT-PCR to page 1001, column 1)

(c) determination of the signal associated with the reporters released due to the 5' polymerase nuclease activity (page 998, figure 3).

With regard to claim 4, Gibson teaches a 24 nucleotide competitor probe which falls within the 1-30 nucleotide claimed range (see table 1, page 1000).

With regard to claim 5, Gibson teaches probes which are 3' end blocked by Tamra (see table 1, page 1000).

With regard to claim 6, Gibson teaches DNA probes and primers (see table 1, page 1000) as well as a thermostable DNA polymerase with 5'-3' exonuclease activity (see page 1000, column 2, subheading "QC RT-PCR").

With regard to claim 7, in Table 1, on page 1000, primer P1 has a calculated Tm of 65 C, primer P2 has a calculated Tm of 65 C, while probe 6 has a calculated Tm of 67 C and probe 7 has a calculated Tm of 69 C. So the probes have a higher Tm than the primers.

With regard to claim 8, Gibson teaches a 24 nucleotide competitor probe which falls within the 18-30 nucleotide probe range claimed (see table 1, page 1000).

With regard to claim 9, Gibson teaches probes with a quencher label (see table 1, page 1000).

Gibson does not teach addition of the calibrator prior to the extraction procedure. Gibson does not expressly teach that the Tm should be kept as identical as possible.

WalkerPeach teaches a method of using an internal control to monitor nucleic acid amplification assays (see column 1, lines 50-65) where the internal control can be added either before or after extraction (see column 14, lines 30-32). WalkerPeach

teaches that the internal control will have the identical sequence in an inverted orientation to create a control sequence which will have identical nucleotide composition with the sample and identical Tm (see column 5, lines 21-26) which addresses the limitations of claims 1-3. In particular, WalkerPeach teaches "The present invention allows an investigator to control for inhibition of a sequence amplification reaction with a control sequence that has the same Tm as the target sample (column 5, lines 62-64)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the internal control of WalkerPeach in the method of Gibson since WalkerPeach notes "This quantitative sequence similarity between target and control ICC sequences provides a number of advantages over conventional methods. For example, since the amplified sequences of the target and control plasmids are of the same length and composed of the same nucleotide bases, the reaction parameters for the two plasmids are identical. Reaction parameters such as the Tm, the length of the sequence amplified, primer annealing or hybridization and primer usage are all substantially the same for the experimental and control sequences of the present invention. Given the similarity in reaction parameters between the two sequences, the yield of the co-amplification reactions should also be similar. Thus the inverted sequence of the control plasmid provides an extremely valid method for investigators to monitor for inhibition during signal amplification reactions. (see column 5, lines 46-60)". Further, WalkerPeach expressly motivates the use of this internal control into a broad range of amplification assays, noting "The present invention contemplates utility for use as an internal inhibition control in a variety of signal amplification assays. Examples of

signal amplification assays include: the polymerase chain reaction (PCR), variations of PCR, including reverse transcriptase PCR, real-time PCR, branched DNA (bDNA) assays, nucleic acid sequence based amplification assays (NASBA), transcription mediated amplification (TMA), cytoflowmetric assays, molecular beacon assays, hydridization reactions, and detection assays (see column 4, lines 10-18)".

An ordinary practitioner would have been motivated to modify the method of Gibson to use the internal control of WalkerPeach for the expressly identified advantages of providing an extremely valid method which minimizes variation in reaction parameters. Further, an ordinary practitioner would have been motivated to follow the express guidance of WalkerPeach in adding the internal control before extraction in order to accurately assess the amount of nucleic acid present prior to extraction.

10. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al (Genome Research (1996) 6:995-1001) in view of WalkerPeach et al (U.S. 6,395,470) and further in view of Kennedy et al (J. Pathol. (1997) 183:447-452).

Gibson in view of WalkerPeach teach the limitations of claims 1-9 as discussed above. Gibson in view of WalkerPeach do not teach application of Taqman to HHV-8.

Kennedy teaches application of the Taqman assay, with controls, to detection of HHV-8 (see abstract, page 449, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the internal control method of Gibson in view of WalkerPeach in the detection of HHV-8 as taught by Kennedy since WalkerPeach expressly motivates the use of this internal control into a broad range of amplification assays, noting "The present invention contemplates utility for use as an internal inhibition control in a variety of signal amplification assays. Examples of signal amplification assays include: the polymerase chain reaction (PCR), variations of PCR, including reverse transcriptase PCR, real-time PCR, branched DNA (bDNA) assays, nucleic acid sequence based amplification assays (NASBA), transcription mediated amplification (TMA), cytoflowmetric assays, molecular beacon assays, hydridization reactions, and detection assays (see column 4, lines 10-18)". An ordinary practitioner would have been motivated to modify the method of Kennedy to utilize an internal control in order to maximize the sensitivity and specificity of the assay, which is a particular concern of Kennedy (see page 451, column 2).

***Allowable Subject Matter***

11. Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. The following is a statement of reasons for the indication of allowable subject matter: Claim 14 is drawn to specific probes. While the specific primers and probe for HHV-8 are prima facie obvious over the HHV-8 sequence, the particular calibrator

sequence chosen is unobvious, since there is no specific motivation to design this particular calibrator with it's particular randomized sequence.

***Response to Declaration***

1. The Declaration under 37 CFR 1.132 filed April 25, 2003 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 103 as set forth in the last Office action because:

The Declarant states that an experiment was performed in which the calibrator probes were modified to deliberately fail to meet the requirements of the Taqman probe as determined using the primer express software. The Declarant then states that these modified probes fail to operate in the detection assay system.

This declaration is not found persuasive in showing an unexpected result for several reasons. First, the claims are not commensurate in scope with the declaration. The claims do not require, for example, a G at the beginning of the probe, so this alteration is not commensurate in scope. Second, the suggestive power and evidence of the declaration are weighted against the teachings of the reference. Here, Gibson is not a hypothetical proposed method that was never performed but rather Gibson shows an actual experiment which experiment demonstrated success. So when weighing the evidence, the evidence that a particular altered form of the probes, altered against the teachings of the prior art on which Gibson relies, such as Livak et al, carries little suggestive power. Gibson rests upon a foundation of prior art in the Taqman assay. When Applicant performs an experiment which ignores the teachings of the prior art upon which Gibson rests, the experiment does not show an unexpected result, but

rather shows the expected result which would occur when the prior art teachings on Taqman assays are ignored. Finally, the Primer-express software is itself prior art against this Application and selection of primers for Taqman assays using that software would not be unexpected.

***Response to Arguments***

2. Applicant's arguments filed April 25, 2003 have been fully considered but they are not persuasive.

Applicant argues that the Declaration overcomes the 103 rejection. For the reasons given above, that argument is not found persuasive.

Applicant then argues that the combination is improper because the Walker-Peach calibrator is used for PCR assays other than Taqman PCR. This argument is not found persuasive because both references are in the same narrow art, the use of internal controls in types of PCR amplification assays. There are few ways, apart from a 102, that the references could be closer in concept. With regard to the cited patent, it is noted that Gibson expressly cites the related paper to Holland et al in PNAS which teaches the Taqman assay.

Therefore, the arguments will be maintained.

***Conclusion***

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

June 19, 2003